

Remarks

Claims 1-21 and 23-38 are pending in this application. Claim 22 has been withdrawn from consideration. The pending claims have all been rejected for obviousness. Applicants respectfully request reconsideration of the claims in light of the following remarks.

§ 103 Rejections

Claims 1-21 and 23-38 stand rejected under 35 USC § 103(a) as being unpatentable over Garbe et al. (WO 96/08229) in view of Cleary (EP 0483105 A1). The Examiner asserts that it would have been obvious to one of skill in the art to combine the teachings of these references to arrive at the claimed invention. Applicants respectfully disagree.

In order to establish a *prima facie* case of obviousness, the Patent Office must demonstrate that (1) there is a suggestion or motivation in the prior art to modify or combine reference teachings, (2) one skilled in the art would have had a reasonable expectation of success in making the modification or combination, and (3) the prior art reference(s) disclose all of the claim limitations. The fact that one of ordinary skill in the art would have had the capability to modify the method disclosed in the prior art reference(s) is not sufficient. MPEP 2143.01. The prior art reference(s) must provide a motivation or reason for making the changes. MPEP 2142; *Ex parte Chicago Rawhide Manufacturing Co.*, 226 USPQ 438 (PTO Bd. App. 1984).

Garbe describes a transdermal drug delivery device that comprises a macromer-containing acrylate or methacrylate copolymer, a softener, and a drug. As the Examiner has acknowledged, Garbe does not disclose the specific concentration range of drug recited in the present claims (i.e. about 8% to about 30% by weight), nor does it teach specifically that fentanyl is the drug delivered (Office Action, p. 3).

Garbe teaches that, in general, the drug is present in the device in an amount from about 0.1% to about 30% (page 13, lines 16-18). Garbe also teaches that the drug is preferably fully dissolved, free of solid undissolved drug (page 13, lines 18-20). Garbe, however, provides a very long list of possible drugs for use in the device (pages 12-13), and expressly states that the exact amount of drug that would be suitable for use in the device will vary depending on which specific drug is selected, as well as several other factors, such as the condition being treated and

the surface area of skin to which the device is applied (page 13, lines 9-14). One skilled in the art would understand that the amount of drug that is able to be dissolved in the composition will vary depending on the specific active ingredient chosen, and not all of the drugs listed in Garbe would be expected to be completely dissolved across the entire concentration range disclosed by Garbe.

In the case of Fentanyl, this drug is known to be very difficult to solubilize in acrylate compositions, such as those described in Garbe. In a previous reply dated March 17, 2003, Applicants submitted Exhibit A, an article by Roy et al., and explained how it demonstrated that fentanyl is very difficult to incorporate into a drug delivery composition, particularly an acrylate composition, in amounts greater than 5% by weight. Since Garbe teaches that the drug incorporated into the delivery device should be fully dissolved, one skilled in the art would not have been motivated to use fentanyl in amounts greater than 5%, because a substantial amount of undissolved drug would have been expected to be present at these higher concentrations.

Moreover, given the well-known difficulties associated with solubilizing fentanyl, even if one had been motivated to use a higher concentration of the drug, there would have been no expectation of success in incorporating fentanyl into the Garbe device in the amounts recited in the present claims while still providing a composition that was substantially free of undissolved drug. Garbe teaches that the drug is preferably fully dissolved, but there is nothing in Garbe to suggest that Fentanyl in particular could be successfully formulated in an acrylate composition in amounts between about 8% and about 30% without the presence of a substantial amount of undissolved fentanyl.

The Cleary reference does not compensate for the deficiencies of Garbe. Cleary describes a transdermal drug delivery device comprising fentanyl and absorption enhancers in a matrix. The Examiner has acknowledged that, as with Garbe, Cleary also does not teach the specific concentration range recited in the present claims. Thus, the prior art references, even in combination, do not teach all of the claim elements. Nevertheless, the Examiner asserts that the claimed invention is obvious because it is not inventive to discover optimum or workable ranges by routine experimentation.

The present invention involves much more than merely the discovery of optimum workable ranges for transdermal delivery of fentanyl. It provides for the first time a transdermal

delivery composition in which fentanyl has been incorporated into the composition at relatively high levels (about 8% to about 30% by weight) in solubilized form, substantially free undissolved fentanyl. This allows for delivery of fentanyl over a relatively extended period of time (for example, about 0.5 to about 5.0 mg/day thus resulting in a serum concentration of about 0.2 to about 10 ng/mL for a period of time from about 4 to about 14 days, as recited in claim 30). Although Cleary states that patches containing fentanyl can be worn for 7 days, there is nothing in the cited references that teaches or suggest that the combination of components recited in the present claims would be capable of providing this range of fentanyl, nor the enhanced level of delivery possible with the present invention.

In sum, the present claims are patentable over the cited references because one of ordinary skill in the art would not have been motivated to incorporate fentanyl in an amount of about 8% to about 30% by weight into an acrylate composition in view of the art-recognized difficulties with solubilizing this drug, nor would one have had an expectation of success in producing a composition comprising this amount of fentanyl that was substantially free of undissolved drug. Applicants, respectfully submit that the rejection of claims 1-21 and 23-30 under 35 USC § 103(a) as being unpatentable over Garbe in view of Cleary has been overcome and should be withdrawn.

CONCLUSION

In view of the foregoing remarks, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested.

All communications in this case should be direct to the undersigned. If the Examiner believes a telephone discussion would be helpful to resolve any of the outstanding issue in this case, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Date

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